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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,923	02/20/2001	Roland M. Wenger	6-1032-150	8296

803 7590 10/01/2002

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,923	WENGER ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-14* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Applicants' claim for foreign priority under 35 U.S.C. 119 (a)-(d) in the declaration is acknowledged. Preliminary amendment filed 29 March 2001 prior to patent examination as to cancellation of claims 1-7 and addition of new claims 8-14 has been entered. Thus, Claims 8-14 are pending and examined in this Office action.

Drawing

The drawings are objected to under 37 CFR 1.84(h)(5) because Figure 1-3 show(s) modified forms of construction in the same view. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect may be deferred until after the examiner has considered the proposed drawing correction. Failure to timely submit the proposed drawing correction will result in the abandonment of the application.

Object to IDS

Please note that Applicants' submission of IDS filed 9 June 2000 is incomplete since it contains no legible copies of each U.S. and foreign patent and each publication or that portion, which caused it to be listed as cited in the list of the submitted IDS. Thus, it fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of

submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C (1). Yet, examiner has reviewed all US patent documents listed in the IDS by applicants and herewith provided one of each copy of the patent documents.

Specification Objections

The disclosure is objected to because of the following informalities:

In page 1, line 6, the term "are" should be changed to "is".

In page 3, line 25, "Gag" should be spelled out in full at the first instance of use. See also, page 4, line 7, "HIV-1"; page 6, line 2 for "MeBmt", line 3 for "Abu" and "Nva", line 4 for "Sar", "MeSer", "MeAla" and "Oacyl", line 9 for "Et"' and line 22 for "N-alkyl" and "aa^4"; page 7, line 6, "CaN"; page 10, line 20, "OtBu"; and page 17, line 15, 'CEM-SS".

In page 3, lines 12-13, "...intracellular proteic receptor, cyclosporin A (CyP) forming..." should be changed to "...intracellular proteic receptor (CyP), cyclosporin A forming...".

In page 17, line 19, "2.10^{-6} molar" should be changed to 2×10^{-6} molar.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite in recitation "U is – Abu, Nva, Val, Thr"; the recitation is incomplete as to whether or not there are more amino acid residues than recited in the position "U". See also the recitation "*Z is (N-R)aa where aa = { Val, Ile, ...PheCH (G_3), Tyr (OG_3)} ...*", especially see inside the parenthesis of the recitation. Also, laim1 is unclear as to whether or not "(N-R) aa" refers to N-alkylation at position 4 amino acid (aa) wherein R is an alkyl group and N" is an α-amine a part of the peptide bond that forms between residue Z with adjacent one Y, or, amino acid (aa) is linked to R (alkyl) group while "N" therein a tetra-amine that forms amide bonds with adjacent amino acid residues. See also Claim 11. Further, Claim 1 is unclear in the recitation "G_1 = {phenyl-COOH, Phenyl-COOMe, phenyl-COOEt}", which appears to be incomplete as well and "or" appears missing between "Phenyl-COOMe" and "phenyl-COOEt". See also "G_3 = {$PO(OH)_2$, $PO(OCH_2 CH=CH_2)_2$, CH_2COOH, $CH_2COOMe(Et)$}". The recitation of Claim1 is unclear as to a semicolon " ; " between CH_2 $COOMe(Et)_4$ and $CH_2PO(OMe)_2$. The dependent claims are also rejected as they do not address ambiguity of Claim 1.

Claim 9 is indefinite as to whether or not the recitation "(R) Val" refers to Valine is linked to R(alkyl) group or R (alkyl) group is conjugated to α-N of Valine residue.

Claim 10 is indefinite as to whether or not "N-ethyl-Val" refers to Valine residue covalently linked to ethyl group or ethyl group conjugation to α-N of Valine residue at position 4 of the cyclosporin molecule.

Claim 12 recites "wherein it is ...": it is not apparent as to what "it" refers to.

Claim 13 is indefinite as to the recitation "intended": is the claimed medicinal product proposed to be used rather than actually for the treatment of AIDS? See also Claim 14. Also,

Claim 13 is awkward as to a comma "," between "AIDS" and "containing"; deletion of the comma is suggested.

Claims 13 and 14 contain "for use..." type language in the recitation of "... intended for treatment..." but the claim (Claim 14) is unclear as to how the intended use alters the medicinal product.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The Claims 8-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Steiner J. P. et al. (US Pat. No. 6444643).

Steiner et al. teach a cyclosporin compound that reads on the structure set forth in Claim 8 of the instant application, i.e. positions 1 through 11 have (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt), α-aminobutyric acid (Abu), sarcosine (Sar), an amino acid residue with alkylation (e.g. C3-C8), e.g. alkylation at α- amine group, Val, MeLeu, Ala, D-Ala, MeLeu, MeLeu and MeVal, respectively (see formula IV and column 10), as applied to Claims 8 of the instant application.

Also, Steiner et al. disclose that the position 4 residue of the cyclosporin structure undergoes alkylation, e.g. N-alkylated Valine (see column 11, line 18 and formula IV at column 10), and typically the alkyl chain has a range from C3 to C8 (see column 10, lines 15-20), as applied to Claims 9 and 10 of the instant application.

Further, Steiner et al. teach formulation of the claimed cyclosporin into the pharmaceutical composition (see columns 5-6), as applied to Claims 11 and 12 of the instant application. Note that Claims 13-14 refers to intended use of the cyclosporin; thus, the claims are also included in the rejection.

Therefore, the disclosure of Steiner et al. anticipates the subject matter of Claims 8-14 of the current application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have

been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-14 are rejected under 35 U.S.C. 103(a) as being obvious over Ko, S. Y. et al. (US Pat No. 5767069) taken with Steiner, J. P. et al (US Pat. No. 6444643).

Ko (US Pat No. 5767069) et al. teach a synthesized cyclosporin compound in which at positions 1 through 11 have (4R)-4-[(E)-2-butenyl]-4-methyl-L-threonine (MeBmt), α-aminobutyric acid (Abu), sarcosine (Sar), an N-alkyl (methyl)modified amino acid (MeIle), Val, MeLeu, Ala, D-Ala, MeLeu, MeLeu and MeVal, respectively (see Claim 1, column 5and formula I), as applied to Claim 1 of the instant application.

Also, Ko (US Pat No. 5767069) et al. teach a pharmaceutical composition comprising the cyclosporin as set forth above (see Claim 4), as applied to Claims 12 and 13 of the current application.

Further, Ko (Us Pat. No. 5767069) et al. teach an active cyclosporin compound for anti-HIV i.e. treatment of AIDS (see example 12, Claim 4, columns 3 and 4, and column 5, lines 1-6), as applied to Claims 12 and 13 of the instant application.

However, Ko (US Pat No. 5767069) et al. do not teach amino acid residue at position 4 of the cyclosporin is the amino acid in which α amine is conjugated to an alkyl group (e.g. ethyl group) higher than methyl group.

Steiner et al. teach a cyclosporin compound that reads on the structure set forth in Claim 8 of the instant application and is identical to the structure disclosed by Ko (US Pat No. 5767069) which are used as a pharmaceutical composition for treating HIV disease (see formula IV at column 9), as applied to Claims 8 and 11-13. Also, Steiner et al. teach the position 4 of the cyclosporin compound is subject to alkylation (C3-C8) (see column 10, lines 12-20), as applied to claim 9 of the instant application. In addition, Steiner et al. teach N-alkylation for Valine derivative (i.e. position 4 is N-ethyl Valine), as applied to Claims 10 and 14 of the instant application. Yet, Steiner et al. do not expressly disclose using cyclosporin for treatment of AIDS disorder.

One of ordinary skill in the art would have combined the teachings of Ko et al. and Steiner, et al. for the following advantages: (*a*) various modifications of position 4 of cyclosporin retains biological activities of the modified compounds as taught by Ko et al. (see column 5, lines 7-9); and (*b*) derivatives and analogue of cyclosporin, e.g. N-alkylated Valine at position 4, lack immunosuppressive effect, which is an important factor for therapeutic use of the synthesized nonimmunosuppressive cyclosporin variant in treatment of disorder state, e.g. AIDS as taught by Steiner et al. (see column 11, lines 11-23).

Given the above motivation one of ordinary skill in the art would have combined the teachings of Ko et al. and Steiner et al. with respect to development of a therapeutic composition for treating HIV-infection comprising modification at position 4 of the cyclosporin compound, e.g. N-ethyl Valine, or other types of N-alkylated amino acid derivatives and testing for their anti-HIV activities, which are based on the cyclosporin disclosed in the art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

CHRISTOPHER S F LOW
SUPERVISORY PATENT EXAMINER
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September 18, 2002